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MECHANISMS UNDERLYING IMMUNOTHERAPY TRIALS IN AUTOIMMUNITY

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National Institute of Allergy and Infectious Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Office of Research on Women's Health

Letter of Intent Receipt Date: January 15, 1995
Application Receipt Date: March 21, 1995

PURPOSE

The National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the Office of Research on Women's Health (ORWH) of the National Institutes of Health invite applications for research into the basic mechanisms underlying new immunotherapies being tested for the prevention and treatment of various autoimmune diseases. Human clinical trials of new and innovative therapies for autoimmune disease are proceeding even though the exact mechanisms of the interventions being tested are unknown. This Request for Applications (RFA) seeks studies that would expand the clinical evaluation of these experimental treatments by incorporating basic research on the molecular and immunologic mechanisms underlying these immune therapies. By augmenting the clinical investigations with research designed to elucidate specific mechanisms of action,

assessment of clinical outcomes will be more meaningful and could facilitate the development of future therapeutic strategies.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This RFA, Mechanisms Underlying Immunotherapy Trials in Autoimmunity, is related to the priority area of diabetes and chronic disabling diseases. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0) or "Healthy People 2000" (Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone (202) 782-3238).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private institutions, such as universities, colleges, hospitals, laboratories, units of State or Local governments, and eligible agencies of the Federal government. Foreign institutions are not eligible to apply for First Independent Research Support and Transition (FIRST) (R29) awards. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISM OF SUPPORT

The mechanisms of support will be the individual research project grant (R01) and the FIRST (R29) award. The total project period for applications submitted in response to this RFA may not exceed five years; foreign applications may not request more than three years of support. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant.

This RFA is a one-time solicitation. Future competing renewal applications will compete with all investigator-initiated applications and will be reviewed according to customary referral and review procedures.

FUNDS AVAILABLE

The estimated funds available for the total (direct and indirect) first-year costs of all awards made under this RFA will be $750,000 from NIAID, $250,000 from NIDDK, $250,000 from NIAMS, and $200,000 from ORWH. In Fiscal Year 1996, the NIAID plans to fund approximately four R01/R29s, NIDDK one R01/R29, NIAMS one R01/R29, and ORWH one R01/R29. The usual PHS policies governing grants administration and management will apply. This level of support is dependent on the receipt of a sufficient number of applications of high scientific merit. Although this program is provided for in the financial plans of the Institutes, awards pursuant to this RFA are contingent upon the availability of funds for this purpose. Funding beyond the first and subsequent years of the grant will be contingent upon satisfactory progress during the preceding years and availability of funds.

RESEARCH OBJECTIVES

Background

Autoimmune diseases are a significant source of morbidity, often severe, in the U.S. population, costing billions annually in health care expenditures and lost productivity. Many of these diseases, including Systemic Lupus Erythematosus, Rheumatoid Arthritis and Multiple Sclerosis, disproportionately affect women rather than men. One hypothesis for the pathogenesis of these diseases is that there is failure of the normal process of self-tolerance. Studies of these diseases in animal models suggest that tolerance to self antigens can be induced by the oral or peripheral presentation of various antigens with a reduction in the incidence of the disease. Several preliminary trials in humans have also suggested that these diseases may be ameliorated or prevented with antigen based therapy. Based on these interesting results, clinical trials in humans have begun in patients with Insulin-Dependent Diabetes Mellitus, Multiple Sclerosis, and Rheumatoid Arthritis to determine if these diseases can be prevented or treated with immunotherapy. Other new innovative therapies of autoimmune disease directed at modulation of the immune system are also being tested, including treatment of Rheumatoid Arthritis patients with monoclonal or chimeric antibodies directed against TNF-` or adhesion molecules or non-depleting CD-4 antibodies or administration of collagen peptides to patients with scleroderma.

Research Objectives and Scope

This RFA seeks to support hypothesis-driven basic research projects investigating molecular and cellular mechanisms underlying changes in the immune response and clinical outcome in patients enrolled in large scale, funded clinical trials of the efficacy of immunotherapies to treat or prevent autoimmune disease. By augmenting ongoing clinical studies, the NIH seeks to take advantage

of these unique clinical populations to gain valuable insights into autoimmunity. Examples of ongoing clinical trials appropriate for studies of basic underlying mechanisms include, the Diabetes Prevention Trial - Type 1, to test the administration of a self antigen (insulin), either orally or subcutaneously, in preventing development of diabetes; and clinical trials testing the oral administration of chicken Type II collagen for the treatment of Rheumatoid Arthritis and oral administration of myelin for the treatment of Multiple Sclerosis. However, basic research projects linked to large-scale, funded human trials of other innovative immunotherapies for the prevention/treatment of autoimmune disease are also be appropriate for this RFA. Studies related to clinical trials evaluating the use of immunosuppressive drugs for the prevention/treatment of autoimmune disease are NOT within the scope of this RFA.

The NIH is interested in increasing understanding of the immunological mechanisms underlying these new innovative therapies for autoimmune disease. The specific research approach proposed in each application will be dependent on the particular intervention utilized in the trial. Examples of possible relevant hypothesis-driven research topics include, but are not limited to, assessments of alterations in relevant molecular and cellular aspects of the immune response such as:

o Evaluation of responses to disease-related and control antigens in helper T cells, suppressor T cells, B cells, and inflammatory cells

o Studies of disease-related antibody responses and/or disease-related activation of other mediators of the immune and/or inflammatory responses

o Investigations of antigen presentation and tolerance induction/maintenance and studies of molecular mechanisms of cell activation

o Effects of immunotherapy on cell trafficking and migration and the production and activity of the molecular mediators of relevant responses

Hypothesis-driven studies of cell populations whose presence or activity correlates with activity of disease would be particularly useful. These examples are not intended to be all encompassing or limiting. Studies in animals that parallel the human clinical trials WILL NOT be considered responsive. Close collaboration between clinical and basic scientists in the planning and implementation of these research studies is highly encouraged.

NOTE: Investigators proposing to utilize the patient populations from clinical trials must obtain permission from the ancillary studies committees of the appropriate trial. Applications must include evidence that approval has been applied for and written approval by the appropriate Study Group of the ongoing trial for which basic research studies are being proposed under this RFA must be provided by the time the application is reviewed.

NOTE: Investigators interested in developing small basic research projects ($50,000 - Direct Costs) linked to clinical trials should look for the soon to be issued NIAMS-sponsored RFA "Small R01 Program for Mechanisms of Immunotherapy in Rheumatic Diseases".

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This new policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43) and supersedes and strengthens the previous policies (Concerning the Inclusion of Women in Study Populations, and Concerning the Inclusion of Minorities in Study Populations) which have been in effect since 1990. The new policy contains some new provisions that are substantially different from the 1990 policies.

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which has been published in the Federal Register of March 28, 1994 (FR 59 14508-14513), and reprinted in the NIH GUIDE FOR GRANTS AND CONTRACTS of March 18, 1994, Volume 23, Number 11.

Investigators may obtain copies from these sources or from the program staff or contact person listed below. Program staff may also provide additional relevant information concerning the policy.

LETTER OF INTENT

Prospective applicants are asked to submit, by January 15, 1995, a letter of intent that includes a descriptive title of the overall proposed research, the name, address and telephone number of the Principal Investigator, and the number and title of this RFA.

Although the letter of intent is not required, is not binding, does not commit the sender to submit an application, and does not enter into the review of subsequent applications, the information that it contains allows NIAID staff to estimate the potential review workload and to avoid conflict of interest in the review. The letter of intent is to be sent to Dr. Olivia Preble at the address listed under INQUIRIES.

APPLICATION PROCEDURES

Applications are to be submitted on the standard research grant application form PHS 398 (rev. 9/91). These application forms may be obtained from the institution's office for sponsored research or its equivalent and from the Office of Grants Information, Division of Research Grants, National Institutes of Health, 5333 Westbard Avenue, Room 449, Bethesda, MD 20892, telephone (301) 435-0714. For purposes of identification and processing, item 2a on the face page of the application must be marked "YES" and the RFA number and the words "MECHANISMS UNDERLYING IMMUNOTHERAPY TRIALS IN AUTOIMMUNITY" must be typed in.

It is highly recommended that the NIAID program staff, listed under INQUIRIES, be consulted before submitting the letter of intent and during the early stages of preparation of the application. Applications that do not conform to the instructions contained in PHS 398 (rev. 09/91) application kit, will be judged nonresponsive and will be returned to the applicant.

The RFA label available in the PHS 398 must be affixed to the bottom of the face page. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. FIRST award (R29) applications must include at least three sealed letters of reference attached to the face page of the original application. FIRST applications submitted without the required number of reference letters will be considered incomplete and will be returned without review.

Applications must be received by March 21, 1995. Applications received after the receipt date will be returned without review. The Division of Research Grants (DRG) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. This does not exclude the submission of substantial revisions of an application already reviewed. These applications must, however, include an introduction addressing the previous critique.

Submit a signed, typewritten original of the application, including the checklist, and three signed, exact, single-sided photocopies, in one package to:

Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, MD 20892**

At the time of submission, two additional exact copies of the grant application and all five sets of the appendix must also be sent to Dr. Olivia Preble at the address listed under INQUIRIES.

Applicants from institutions THAT have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC program director or principal investigator could be included with the application.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the DRG and for responsiveness by NIAID staff. Incomplete and non-responsive applications will be returned to the applicant without further consideration.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NIAID in accordance with the review criteria stated below. As part of the initial merit review, a process (triage) may be used by the initial review group in which applications will be determined to be competitive or non-competitive based on their scientific merit relative to other applications received in response to the RFA. Applications judged to be competitive will be discussed and be assigned a priority score. Applications determined to be non-competitive will be withdrawn from further consideration and the principal investigator and the official signing for the applicant organization will be promptly notified. The second level of review will be provided by the National Advisory Allergy and Infectious Diseases Council.

Review Criteria

o scientific, technical, or medical significance and originality of proposed research;

o appropriateness and adequacy of the experimental approach and methodology proposed to carry out the research;

o qualifications and research experience of the Principal Investigator and staff, particularly, but not exclusively, in the area of the proposed research;

o availability of the resources necessary to perform the research;

o appropriateness of the proposed budget and duration in relation to the proposed research;

o adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

For foreign applications, in addition to the above criteria, the reviewers will be asked to comment on the availability of special opportunities for furthering research programs through the use of unusual talent resources, populations, or environmental conditions that are not readily available in the United States or which provide augmentation of existing U.S. resources.

The initial review group will also examine the provisions for the protection of human and animal subjects and the safety of the research environment.

AWARD CRITERIA

Funding decisions will be made on the basis of scientific and technical merit as determined by peer review, program priorities, and the availability of funds.

INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged.
The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Elaine Collier, M.D.
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases

Solar Building, Room 4A20
6003 Executive Boulevard
Bethesda, MD 20892-7640
Telephone: (301) 496-7104
FAX: (301) 402-2571
Email: EC5X@NIH.GOV

Joan T. Harmon, Ph.D.
Division of Diabetes, Endocrinology, and Metabolic Diseases
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Natcher Building, Room 5AN-18G
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Susana Serrate-Sztein, M.D.
Rheumatic Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building, Room 5AS-376
45 Center Drive MSC 650
Bethesda, MD 20892-650
Telephone: (301) (301) 594-5032
Email: arthrit@ep.niams.nih.gov

Direct inquiries regarding review issues, mail two copies of the application and all five sets of appendices, and mail letter of intent to:

Olivia T. Preble, Ph.D.
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Solar Building, Room 4C19
6003 Executive Boulevard
Bethesda, MD 20892-7610
Telephone: (301) 496-8208
FAX: (301) 402-2638
Email: OP2T@NIH.GOV

Direct inquiries regarding fiscal matters to:

Ms. Jacqueline Johnson
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Solar Building, Room 4B26
6003 Executive Boulevard
Bethesda, MD 20892-7610
Telephone: (301) 496-7075
Email: JJ19E@NIH.GOV

Schedule

Letter of Intent Receipt Date: January 15, 1995
Application Receipt Date: March 21, 1995
Scientific Review Date: June/July 1995
Advisory Council Date: September 1995
Earliest Award Date: December 1995

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance, No. 93.855, No. 93.847, and No. 93.361. Awards will be made under the authority of the Public Health Service Act, Title IV, Part A, (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The Public Health Service (PHS) strongly encourages all grant recipients to provide a smoke-free work place and promote the nonuse of all tobacco products. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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